REMARKS / ARGUMENTS

By the present amendment, claims 1 and 22 have been amended as described below and claim 12 has been amended to specify that the method of claim 12, when used with the system of claim 1, forms T cells of one or more of the following lineages: (a) TCR-$\alpha\beta^+$ $CD4^-CD8^+$ T cells; and/or (b) TCR-$\gamma\delta^+$ T cells. Support for this amendment is found on page 37, lines 16-20 and page 42, lines 1-6. Claims 1, 2, 4, 10-13,17 and 22 are pending in the application. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants reserve the right to pursue any of the deleted subject matter in a further continuation, continuation-in-part or divisional application. The amendment does not contain new matter and its entry is respectfully requested.

The final office action dated March 6, 2007 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 USC § 112, first paragraph

The Examiner has rejected claim 22 under 35 USC §112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner considers recitation of "TCR-$\alpha\beta^+CD4^+CD8^+$ double positive T-cell.." to be new matter and adds that Applicants have not indicated where in the specification implicit or explicit support for this limitation can be found.

The Applicant respectfully disagrees that the recitation of "TCR-$\alpha\beta^+CD4^+CD8^+$ double positive T-cell.." is new matter. The Applicant directs the Examiner to page 19 lines 5-18 which states that cells of the T cell lineage may be ... "(e) precursor thymocytes that are $CD4^+CD8^+$ double positive (DP); ... (i) TCR-$\alpha\beta^+$, and/or TCR-$\gamma\delta^+$" (lines 13-16). In

addition, in Example 2 on page 30, line 14, it is stated that $CD4^+CD8^+$ DP T cells are formed using the system. Further, previous Examiner explicitly stated that claim 22 was enabling for an *"in vitro"* system comprising OP9 stromal cells that express Delta-like 1 ligand that supports $\alpha\beta$ $CD4^+$ $CD8^+$ T cells..." (please see page 3 paragraph 1 of office acton issued 01/25/2005). However, in order to expedite prosecution, Applicant has amended claim 22 to recite $CD4^+CD8^+$ double positive T-cells which are supported verbatim by the specification as filed. It is submitted that this amendment does not exclude TCR-$\alpha\beta^+$ DP T cells. In view of the foregoing, we respectfully request that the objection to claim 22 be withdrawn.

35 USC § 112, first paragraph

The Examiner has rejected claims 12-13, 17 and 22 under 35 USC §112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner alleges that the "specification fails to describe cells that are capable to differentiate into T-cells upon transfection or transduction with gene" and that the "specification does not disclose the knowledge in the prior art and/or a description as to the availability of a representative number of species of such stem cells or progenitor cells that are capable of differentiating into cells by transfecting with any gene *in vitro* or *in vivo* that must exhibit the disclosed biological functions as contemplated by the claims".

Claims 12-13, 17 and 22 relate to a method of forming cells of the T cell lineage. The method involves culturing stem cells or progenitor cells that are capable of differentiating into cells of the T cell lineage with the transformed OP9 stromal cells as described in the claims. The Examiner states at page 5 of the office action that the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Applicant is not attempting to claim novel stem cells or progenitor cells. Such cells are known in the art and clearly described in the application to convey to one of skill in the art that Applicant had possession of such

cells. In particular, on page 18, line 7 to page 19, line 4, a definition as well as examples (e.g. hematopoietic progenitor cells, hematopoietic stem cells and embryonic stem cells) of such cells is provided. In addition, the Examples provide clear working examples demonstrating that hematopoietic progenitor cells (HPC) and embryonic stem cells (ESC) are induced to differentiate into T cells using the method of the invention. In this regard, we refer to Examples 2 and 3 on pages 32-35 of the application.

The Examiner also notes that the specification states that the progenitor or stem cells may be genetically modified and comments that "the specification fails to describe cells that are capable to differentiate into T cells upon transfection or transduction with gene." Applicant is not claiming novel cells that have been transfected or transduced. As mentioned above, the claims under objection are method claims that employ stem cells or progenitor cells.

Further, the Applicant respectfully submits that it was well known in the art that stem cells and progenitor cells that are capable of differentiation into cells of the T cell lineage, could be transfected or transduced, and that such transfected or transduced cells, remain capable of establishing cells of the T cell lineage. In this regard, we enclose Verhasselt et al. (Retrovirally transduced $CD34^{++}$ human cord blood cells generate T cells expressing high levels of the retroviral encoded green fluorescent protein marker in vitro. Blood. 1998, 91:431-40) which demonstrated transduction of hematopoietic stem cells ($CD34^{++}Lin^{-}$ and $CD34^{++}CD38^{-}Lin^{-}$ cells) with a Green Flourescent Protein (GFP) lentiviral construct and further showed that such transduced cells remained capable of generating T, NK and dendritic cells in fetal thymus organ culture (see Abstract). GFP is a non-mammalian gene that functions as a marker for identifying transduced cells. Hence, Verhasselt et al. demonstrate that there are no critical structural elements required of the gene to be transduced as GFP in this instance functions only as a marker gene. We also enclose Kaneta et al. (A role for pref-1 and HES-1 in thymocyte development. J Immunol. 2000, 164:256-64) which

demonstrated, using a different T cell subtype, that immature thymocytes can be retrovirally transduced and that such retrovirally transduced thymocytes develop into cells of the T cell lineage. Figures 7E and 7F (Kanata et al. page 262) demonstrate that both GFP transduced thymocytes and Hes-1+GFP transduced thymocytes are capable of developing into cells of the T cell lineage, including $CD4^+$, $CD8^+$ and $CD4^+CD8^+$ double positive T cells (7E), and TCR-β+ and TCR-γ+ T cells (7F). Together, Verhasselt et al. and Kaneta et al., as well as other publications prior to the filing of the present Application, indicate that it was well known that stem cells or progenitor cells capable of forming T cells could be modified by transfection or transduction and differentiate into cells of the T cell lineage.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC § 112, first paragraph be withdrawn.

35 USC § 112, Second Paragraph

The Examiner has objected to claims 1, 2, 4, 10-13, 17 and 22 under 35 USC § 112, second paragraph as being indefinite. In particular, the Examiner alleges that it is unclear what is encompassed by "system".

In response, the Applicant has amended claim 1 to clarify that the *in vitro* system is a system "for forming cells of the T cell lineage from stem cells or progenitor cells". Support for this amendment can be found at page 4 line 25 which indicates the system of the invention is for formation of "cells of the T cell lineage" and page 19 lines 5-18 which describes "cells of the T cell lineage ". Claims 2, 4, 10-13, 17 and 22 depend on claim 1 and thereby incorporate the amendment of claim 1. Applicant respectfully submits that the system claims of claims 1, 2, 4, 10-11 are clearly claims to a product that comprises a cell preparation comprising OP9 stromal cells modified to express a Delta-like-1 or Delta-like-4 Notch ligand. Claims 12-13, 17 and 23 are clearly method claims.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC § 112, second paragraph be withdrawn.

35 USC § 103(a)

The Examiner has objected to claims 1, 2, 4, 12-13 and 17 as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001); Nakano et al (1994, Science 265:5175); and Tatsumi et al (1990, Proc. Natl. Acad. Sci. 87:2750-2754). The Examiner alleges that a practitioner in the art would be motivated to modify the method of Jaleco et al. with the OP9 cells of Nakano et al. in order to reduce the number of inhibitory ligands and to optimize T cell induction.

The Applicant respectfully disagrees. First, Jaleco et al. used a stromal cell line (S17) that was known to induce two cell lineages from CD34+ precursor cells: initially myeloid cells followed by an outgrowth of early B cell progenitors (Rawlings et al. Long term culture system for selective growth of human B cell progenitors Proc Natl Acad Sci 92:1570-74 1995 – see Abstract; reference 27 in Jaleco et al. and herein provided). Myeloid cells typically represented <5% of cultured cells at 6 weeks and no erythroid or T lineage cells were detected (see page 1571, right column, middle paragraph). As S17, the stromal cell line employed by Jaleco et al. reportedly induced fewer cell types than that reported by Nakano et al., which reported induction of erythroid, myeloid and B cells, the Applicant submits that a person skilled in the art would not have been motivated to modify the method of Jaleco et al. with the cells of Nakano et al. as this would not appear to reduce the number of inhibitory ligands as additional cell types are induced. Use of OP9 stromal cells may actually have been expected to introduce additional cell types into the mix.

Secondly, Nakano et al. reports induction of several cell types including B cells, erythroid and myeloid cells (see Abstract). The system of Nakano et al. does not report

the generation of any cell of the T cell lineage. Thus, the Applicant respectfully submits that Nakano et al. cannot provide motivation to modify Jaleco et al. to a person skilled in the art seeking to "optimize T cell induction". There is no teaching that OP9 cells could be useful to optimize T cell induction. Consequently, a person skilled in the art would also not be motivated to use this system to induce T cell development with the precursors taught by Tatsumi et al.

Thirdly, there is no suggestion that reduction of the number of inhibitory ligands is necessary or sufficient for T cell differentiation. The OP9 cells of Nakano et al., which reportedly do not express M-CSF still induced B cell, erythroid and myeloid lineage cells. It is not obvious what effect expression of Delta-like 1 and Delta-like 4 would have in these cells and it is not obvious that reduction of M-CSF, which permitted development of B cell, erythroid and myeloid lineage cells, would "optimize T cell induction". Accordingly, a person skilled in the art would not be motivated to use the progenitors of Tatsumi et al. with such a system.

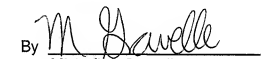
Furthermore, it was unknown prior to the present invention that OP9 cells lacked detectable Delta-like-1 and Delta-like-4 expression (see page 31 lines 21-22 and Figure 1). A person skilled in the art, not having the knowledge that Delta-like-1 and Delta-like-4 expression was absent in OP9 cells would not know why OP9 cells, which support the development of several lineages, do not support T cell differentiation. Consequently a person skilled in the art would have no motivation to modify Jaleco et al. with the OP9 cells of Nakano et al. to produce cells of the T cell lineage. Similarly, a person skilled in the art would have no motivation to use the precursors of Tatsumi et al. with the method of Jaleco et al. modified by using the cells of Nakano et al.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC § 103(a), be withdrawn.

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Once the Examiner has reviewed the response, he is kindly requested to contact Micheline Gravelle at 416-957-1682 as Applicant would like to schedule a telephone interview with the Examiner.

Respectfully submitted,

Thomas M. Schmitt et al.

By 

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